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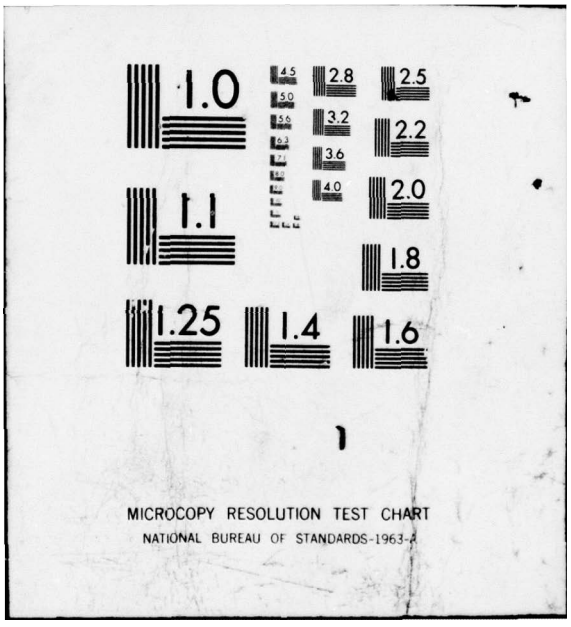
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EDGEWOOD ARSENAL TECHNICAL REPORT

EB-TR-76115

THE EFFECT OF INTRAVENOUS THIAMINE HYDROCHLORIDE ON PRALIDOXIME PHARMACOKINETICS IN MAN

by

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Biomedical Laboratory

December 1976

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Six subjects were given pralidoxime chloride (2-PAMCl) 5 mg/kg, iv, by itself and during a 2.5-hour intravenous infusion of thiamine hydrochloride (100 mg/hr); pralidoxime was given one hour after the infusion was started and the infusion ran 1.5 hours after pralidoxime was given. In the subjects receiving thiamine the plasma concentration of oxime was greater throughout the test period, the renal excretions and clearance of oxime were less during the first 1.5 hours, and the half-life of oxime was prolonged. These data suggest that thiamine inhibits the excretion of oxime, thus prolonging its effects. Whether this will be of value in the therapy of anticholinesterase compound intoxication is unknown.

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PREFACE

The work described in this report was authorized under Project/Task No. 1W762710AD25-02, Medical Defense Against Chemical Agents, Prophylaxis and Therapy for Lethal Agents. This work was started in August 1974 and completed in September 1974.

The volunteers in these tests are enlisted US Army personnel. These tests were governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

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CONTENTS

THE EFFECT OF INTRAVENOUS THIAMINE HYDROCHLORIDE ON PRALIDOXIME PHARMACOKINETICS IN MAN

I. INTRODUCTION

Pralidoxime chloride (pyridine-2-aldoxime methochloride)*, an adjunct to atropine in the treatment of anticholinesterase intoxication, is rapidly and almost completely (80-90%) excreted in the urine[1-6]. This necessitates frequent administration in those circumstances in which a prolonged plasma concentration is desirable.

Swartz *et al.*,[5] recently reported that concurrent intramuscular administration of thiamine hycrochloride with intravenous pralidoxime prolongs plasma half-life and delays the renal elimination of oxime. This suggests that pralidoxime might be handled by the kidney as a strong organic base and might be secreted by the same mechanism by which other strong bases (e.g., thiamine, choline, guanidine, tetraethylammonium) are secreted. Thus, concurrent administration of two bases competing for the same mechanism might lead to delayed secretion of one or both[7].

Those results led us to explore further the clinical use of thiamine hydrochloride to potentiate plasma oxime levels. This report describes the pharmacokinetics of pralidoxime when administered one hour after the start of a continuous infusion of thiamine hydrochloride.

II. EXPERIMENTAL

A. Subjects.

The subjects were US Army enlisted men who agreed to the protocol after thorough explanation and discussion. Screening included complete physical and laboratory examinations**. A detailed history of allergy was obtained and intradermal scratch testing with thiamine was performed to exclude potentially hypersensitive subjects. All scratch tests were negative; two potential subjects were excluded from the study on the basis of a strongly atopic history.

B. Design.

Six subjects participated and received pralidoxime with and without thiamine, each serving as his own control. Subjects entered the ward on the evening before the study, ate a light breakfast about one hour before the study began, and drank about 1 to 2 liters of fluid in the two hours prior to testing. Each subject was tested at one-week intervals in a randomized crossover design plan.

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*Protopam^{R}, Ayerst Laboratories, New York, NY 10017.

**Chest X-ray, ECG, complete blood count, routine urinalysis, blood urea nitrogen, serum creatinine, liver function tests (SGOT, alkaline phosphatase, serum bilirubin).

C. Controls.

At the start of testing, a continuous infusion of normal saline into the anticubital vein was begun and continued for 2.5 hours. One hour after the infusion was started, each subject received an intravenous injection of 5 mg/kg of pralidoxime chloride over two minutes through the scalp needle of the infusion line.

D. Thiamine Treatment.

At the start of testing, a continuous infusion containing normal saline and thiamine hydrochloride* was begun; thiamine was delivered at a rate of 100 mg/hr over 2.5 hours (2.0 mg thiamine/ml normal saline, 50 ml/hr). One hour after the infusion was begun, each subject received an iv injection of pralidoxime, 5 mg/kg, as in the control trial.

Urine from each subject was pooled for the following periods: 0-1.5, 1.5-3, 3-6, and 6-24 hours. Urine was collected for an additional 12 hours from four thiamine-treated subjects. Plasma specimens were obtained through an indwelling scalp needle in a vein in the opposite arm, kept open with heparin, at 0.05, 0.10, 0.15, 0.25, 0.50, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 hours after the injection of oxime. Plasma and urine were analyzed by the method of Groff *et al.*[8] for oxime. Pulse and blood pressure, and subjective responses to both thiamine and pralidoxime, were closely monitored. Subjects were kept in bed during the 2.5-hour infusion; then they were allowed to walk around.

E. Calculations.

The serial plasma oxime concentrations plotted against time fit the curve described by the bi-exponential equation[1]

$$C = Ae^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

which describes the disposition of drug in a two-compartment model. In this equation, C is the plasma concentration, t is the time, A and B represent the zero-time intercepts of the linear components of the rapid and slow portions of the plasma decay curve, and α and β represent the slopes of these two lines divided by -2.303. A more detailed description of the derivation of this equation is provided by Wagner[9] and discussed with respect to pralidoxime in studies by Swartz *et al.*[4,5] and Sidell[1]. The computer program NONLIN[10] was used to estimate the parameters of this equation. From them the following were calculated:

1. The half-life of the rapid equilibrium phase ($t_{1/2\gamma}$) and the slower elimination phase ($t_{1/2\beta}$).

2. The volumes of distribution of the central compartment (V_1), the peripheral compartment (V_2), and the total volume (V_d).

*Thiamine Hydrochloride Injection U.S.P. 10 mg/cc, Natcon Chemical Co., Inc., Plainview, NY.

3. The rate constants for drug movement from central to peripheral compartment (K_{12}), from peripheral to central compartment (K_{21}), and for elimination from the central compartment (K_{13}).

4. The plasma and renal clearances of pralidoxime.

The plasma clearance was calculated by dividing the dose of pralidoxime by the area under the plasma concentration versus time curve (which was obtained from the integral of equation 1); the renal clearance was obtained by dividing the amount of pralidoxime excreted into the urine during a given time period by the area under the curve of that time interval.

F. Complications.

Because of difficulties encountered during administration of oxime to two thiamine-treated subjects, rapid intravenous infusion was not achieved; hence, plasma data on only four thiamine-treated subjects were used for calculations of the parameters listed above compared to control data from six subjects.

Likewise, loss of one urine specimen (1.5-3 hours) from one control subject prevented calculating each parameter.

III. RESULTS

A. Clininal Findings.

Both thiamine and pralidoxime were well tolerated by all subjects. No objective or subjective changes were noted after initiation of thiamine infusion. Following pralidoxime, all subjects complained of mild-to-moderate visual symptoms characterized as "blurring" or visual heaviness, lasting five to 10 minutes. Tests of extraocular muscle movement, accommodation, and light reflex were normal in all men. No changes in blood pressure or pulse rate were noted following oxime injection. Intravenous injection of thiamine did not potentiate any of the subjective experiences and did not alter pulse rate and blood pressure after oxime was given.

B. Plasma Concentration (Six Control Subjects; Four Thiamine-Treated Subjects).

The mean plasma concentrations of pralidoxime are plotted in the following figure. After six minutes, the plasma concentrations of the thiamine-treated group were significantly higher than those of the control group ($p < 0.05$; paired t test) at each time interval during the remaining hours of blood sampling.

C. Urinary Excretion of Pralidoxime.

Over the 24-hour period of urine collection, there was no significant difference in total oxime excretion between the control group and thiamine-pretreated groups. The former excreted 85.7% (±6.2 S.D., n=5) and the latter 87.2% (±5.2, n=6) of the injected pralidoxime. However, in the first 1.5 hours the thiamine-treated men eliminated significantly less oxime

(38.2% vs 72.4% of the total 24-hour urinary oxime excretion, $p < 0.001$, paired t test, n=5) than the subjects in the control group and, in the remaining 22.5 hours, significantly more (46.3% vs 12.8%, $p < 0.01$, paired t test, n=5) (table 1).

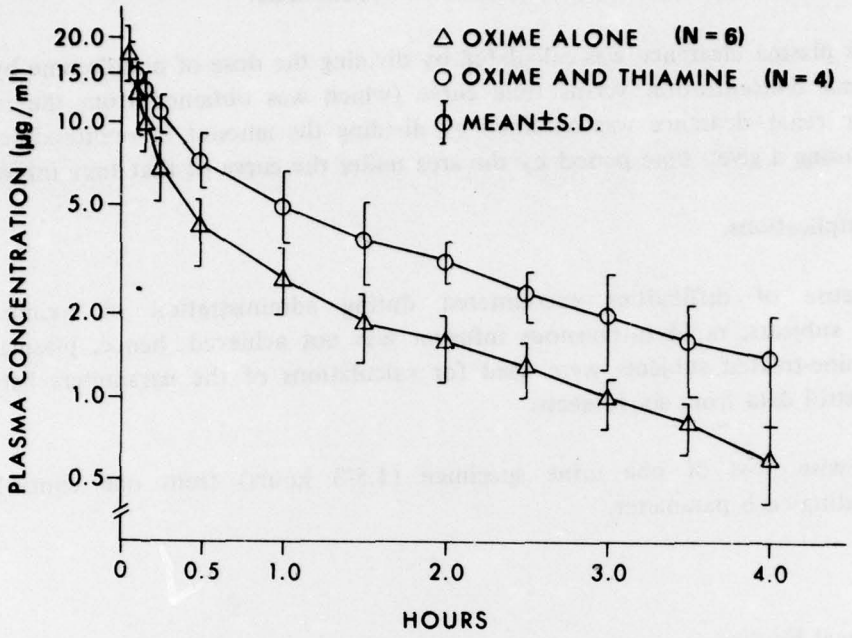

Figure. Mean Plasma Concentrations of Pralidoxime

D. Renal and Plasma Clearance.

Mean renal and plasma clearance data are presented in table 2. The renal clearance of oxime at 1.5 hours was significantly reduced by the simultaneous administration of thiamine ($p < 0.01$, paired t test, n=4), and this maintained over 24 hours. Similarly, the plasma clearance of pralidoxime was greatly reduced by the administration of thiamine ($p < 0.01$, paired t test, n=4).

IV. KINETIC DATA

The kinetic data are shown in table 3.

A. Volumes of Distribution.

Following thiamine administration, there was a definite decrease in the total volume of distribution ($p < 0.05$, paired t test, n=4), characterized by a large decrease in the peripheral (extravascular) volume, V_2 ($p < 0.05$), and a moderate increase in the central compartment ($p < 0.05$).

Table 1. Urinary Recovery of Pralidoxime

(a) Mean Cumulative Excretion of Pralidoxime Over 24 Hours*

	Control	$\bar{P}$ Thiamine	P
0-1.5 hr	72.4 ± 3.3	38.2 ± 9.0	<.001
0-3 hr	87.2 ± 2.4	53.7 ± 4.2	<.01
0-6 hr	97.0 ± 1.0	75.9 ± 8.6	<.01
0-24 hr	100	100	–

* Expressed as percent of the total amount of pralidoxime excreted in the urine ±S.D.

(b) Mean Urinary Excretion of Pralidoxime for Each Collection Period

	Control	$\bar{P}$ Thiamine	P
0-1.5 hr	72.4 ± 3.3	38.2 ± 9.0	<.001
1.5-3 hr	14.8 ± 2.4	15.5 ± 2.1	>.70
3-6 hr	9.8 ± 2.1	22.2 ± 2.2	<.01
6-24 hr	3.0 ± 1.0	24.1 ± 8.6	<.01
Total	100	100	–

Table 2. Renal and Plasma Clearances (ml/min)

Case number	Renal clearance at 1.5 hours		Renal clearance at 24 hours		Plasma clearance	
	c*	t**	c*	t**	c*	t**
6731	477	–	437	–	548	–
6748	502	–	527	–	631	–
6736	546	109	535	253	565	293
6717	515	132	496	216	536	286
6718	574	245	–	441	726	489
6730	717	283	848	350	741	385
Mean	555	205	529	315	625	363
S.D. ±	86.23	97.86	77.06	101.2	90.71	95.20
P†	<0.01		<0.001		<0.01	
n	4		3		4	

* Oxime alone
** Oxime and Thiamine
† Paired t test

Table 3. Pharmacokinetic Constants

Case	A (μg/ml)	α (hr^{-1})	B (μg/ml)	e (hr^{-1})	t ½α (hr)	t ½β (hr)	K_{21} (hr^{-1})	K_{13} (hr^{-1})	K_{12} (hr^{-1})	V_1 (ml/kg)	V_2 (ml/kg)	V_D (ml/kg)
CONTROL												
6731	29.0	9.8	5.4	0.53	0.07	1.30	1.99	2.61	5.69	145	415	560
6748	21.2	11.9	5.8	0.79	0.059	0.88	3.15	2.96	6.53	185	385	570
6736	23.3	8.3	4.6	0.51	0.083	1.25	1.83	2.52	4.52	179	443	622
6717	26.8	10.1	8.1	0.66	0.069	1.05	2.83	2.34	5.56	143	281	425
6718	19.3	9.6	4.7	0.61	0.072	1.14	2.38	2.47	5.38	208	470	678
6730	17.5	10.1	4.4	0.66	0.069	1.05	2.56	2.59	5.57	228	496	
Mean	22.9	10.0	5.5	0.63	0.070	1.11	2.46	2.56	5.54	182	415	597
S.D. ±	4.4	1.1	1.4	0.09	0.01	0.15	0.50	0.21	0.64	33.7	76.5	105
THIAMINE-TREATED												
6731												
6748												
6736	9.8	3.8	8.7	0.47	0.18	1.46	2.08	0.86	1.36	268	175	443
6717	14.0	6.1	10.8	0.42	0.11	1.64	2.87	0.89	2.71	202	191	393
6718	12.4	4.1	5.5	0.47	0.17	1.46	1.59	1.23	1.79	280	319	594
6730	15.7	4.8	5.4	0.42	0.14	1.63	1.53	1.32	2.35	238	364	601
Mean	13.0	4.7	7.6	0.45	0.15	1.55	2.02	1.08	2.05	247	261	508
S.D. ±	2.5	1.0	2.7	0.03	0.03	0.10	0.62	0.23	0.60	34.7	0.924	105.6
p*	0.05	0.001	N3	0.05	0.01	0.02	N3	0.001	0.001	0.05	0.05	0.05

* By paired t test N = 4

B. Plasma Half-Life.

Following thiamine administration, significant increases occurred in both the short half-time, t $1/2\gamma$ (0.07 hr vs 0.15 hr, $p < 0.01$, n=4) and, more importantly, the long half-life of elimination, t $1/2\beta$ (1.11 hr vs 1.55 hr, $p < 0.02$, n=4).

C. Equilibrium Constants.

Likewise, following thiamine, highly significant decreases occurred in the rate constants K_{12} ($p < 0.001$, n=4) and K_{13} ($p < 0.001$, n=4). The change in K_{12} closely parallels the decrease in the peripheral compartment noted above.

V. DISCUSSION

These data indicate that concurrent intravenous administration of thiamine hydrochloride significantly decreases both the renal and plasma clearance and delays the renal elimination of pralidoxime chloride apparently without altering the mode of excretion. Such treatment was associated with substantially higher plasma concentrations of oxime than in the controls throughout the 4-hour period of blood sampling. This study extends the investigation of Swartz *et al.*[5] (who administered thiamine intramuscularly with the oxime) by intravenous pretreatment with the vitamin to achieve and maintain maximal plasma levels at the time of oxime administration.

A dose of 100 mg of thiamine per hour was empirically selected for the pretreatment dose. Neither pharmacokinetic data nor renal tubular secretory transport maxima are available for thiamine, and it is possible that still larger doses of the vitamin would further retard the renal elimination of oxime.

During the 1.5 hours of thiamine administration after injection of pralidoxime, the amount of oxime excreted in the urine was halved. This suggests that prolonging the thiamine infusion at the same rate might have maintained this difference for a longer period of time.

The fractional recovery of oxime in the urine, the plasma half-life for elimination, and the renal and plasma clearances of the drug noted are comparable to those noted previously[1,5]. Swartz[5], however, reported no significant changes in volumes of distribution after intramuscular thiamine administration, though a tendency did appear toward a reduction in the peripheral compartment (V_2)*. In contrast, our data show significant changes in all those volumes (table 3). A definite explanation for this phenomenon is not possible, but the alternatives include: (1) increased protein binding affinity for oxime following thiamine administration (but since pralidoxime is negligibly bound, this seems unlikely); (2) increased sequestration of pralidoxime by other organs (e.g., CNS, liver); and (3) alteration of erythrocytic and/or vascular membrane permeabilities by as yet unknown mechanisms.

*Personal communication.

While this study does not offer proof, these data suggest that pralidoxime may be excreted, at least in part, by a renal secretory mechanism shared by several other strong organic bases[7] although this does not exclude the possibility that several different mechanisms may be involved in the renal elimination of oxime. Ultimate identification of the responsible mechanism will depend upon further studies with specific blockers of secretion and reabsorption as well as the use of micropuncture techniques.

The effect of thiamine in prolonging the plasma half-life of pralidoxime has been demonstrated, although the clinical value of this regimen in the therapy of anticholinesterase poisoning has not been investigated. Thiamine appears well tolerated in pharmacologic doses and has an extremely low incidence of undesirable side effects; however, a few case reports indicate that a rare but fatal allergic reaction to parenteral (particularly intravenous) administration of thiamine may occur and is presumably anaphylactic[11-13].

These results suggest that larger doses of thiamine might produce even larger increases in the half-life of pralidoxime, and it is possible that other strong organic bases with quaternary N^+ sites – such as guanidine, choline, and tetraethylammonium -- might be equally effective. Additional studies are currently under way.

LITERATURE CITED

1. Sidell, F. R., Groff, W. A., and Kaminskis, A. Toxogonin and Pralidoxime: Kinetic Comparison After Intervenous Administration to Man. J. Pharm, Sci., *61*, 1765-9 (November 1972).

2. Kondritzer, A. A., Zvirblis, P., Goodman, A., and Paplanus, S. H. Blood Plasma Levels and Elimination of Salts of 2-PAM in Man After Oral Administration. J. Pharm. Sci., *57*, 1142-6, (July 1968).

3. Loomis, T. A. Distribution and Excretion of Pyridine-2-aldoxime Methodide (PAM); Atropine and PAM in Sarin Poisoning. Toxicol. and Appl Pharmacol., *5*, 489-99 (1963).

4. Swartz, R. D., and Sidell, F. R. Effects of Heat and Exercise on the Elimination of Pralidoxime in Man. Clin. Pharm. Ther., *14*, 83-89 (1973).

5. Swartz, R. D., and Sidell, F. R. Renal Tubular Secretion of Pralidoxime in Man. Edgewood Arsenal Technical Report EB-TR-73017. January 1974. UNCLASSIFIED report.

6. Berglund, F., Elwin, D. E., and Sundwall, A. Studies on the Renal Elimination of N-methyl-pyridinium-2-aldoxime. Biochem. Pharmacol., *2*,383-388 (1962).

7. Peters, L. Renal Tubular Excretion of Organic Bases. Pharmacol. Rev., *12*, 1-35 (1960).

8. Groff, W. A., and Ellin, R. J. A New and Rapid Determination of Pyridinium Aldoximes in Blood and Urine. Clin. Chem. *15*, 72-83 (1962).

9. Wagner, J. C. Pharmacokinetics. J. M. Richard Laboratories, Grosse Pointe, Michigan. 1969.

10. Metzler, C. M. A User's Manual for NONLIN. The Upjohn Company. November 25, 1969.

11. Smith, J. A., Fo, P. P., Weinstein, H. R., Ludwig, A. S., and Weitherion, J. M. Some Aspects of Thiamine Toxicity. J. Pharm. Exp. Ther., *93*, 294-304 (July 1948).

12. Haley, T. J., and Flesher, A. M. A Toxicity Study of Thiamine Hydrochloride. Science, *104*, 567-8 (December 1946).

13. Reingold, J. M., and Webb, F. R. Sudden Death Following Intravenous Injection of Thiamine Hydrochloride. J.A.M.A., *130*, 491-2 (1946).

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